CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40287

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 40-287 Date of Submission: 11/25/97

Applicant's Name: Halsey Drug Company, Inc.

Established Name: Prednisolone Syrup, USP (15mg/5mL)

Labeling Deficiencies:

1. GENERAL COMMENTS:

   i. Replace the "CAUTION: Federal law..." statement with the symbol "Rx only" or "℞ only". We refer you to the Guidance For Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements...", at the internet site, **http://www.fda.gov/cder/guidance/index.htm** for guidance.

   ii. Revise to read "teaspoonful" rather than "teaspoon" when expressing a volume in your insert labeling.

2. CONTAINER- 8 ounce(236 ml) and 16 ounce(473 ml) bottles

   i. Alcohol must be declared in conjunction with the active ingredients. Revise to include the alcohol content of your product in terms of percent volume (v/v) of absolute alcohol. You are referred to section 502(e) of the Act and 21 CFR 201.10(d) (2) for guidance.

   ii. Please assure that the established name and expression of strength appear most prominently on the label.

3. Insert

   a. DESCRIPTION

      i. We encourage you to revise the chemical name to be the same as the second name appearing in the official monograph for prednisolone in USP 23.

ii. Second paragraph, second sentence:

Add a colon after "is". [...formula is:]

iii. Third paragraph, first sentence:

Replace "per" with "in".[..in each 5mL.]

iv. Third paragraph, second sentence:

Begin sentence with "It". [It also contains...]

v. Third paragraph, last sentence:

Replace "sugar" with "sucrose".[..Sodium Saccharin, & Sucrose.]

vi. Refer to comment (i.) under CONTAINER.

b. CLINICAL PHARMACOLOGY

Second paragraph, first sentence:

Do not capitalize "prednisolone". [..as prednisolone cause...]

c. INDICATIONS AND USAGE

i. Under listed subsection 9., Neoplastic Diseases:

Do not capitalize "palliative". [...For palliative management...]

ii. Last sentence following listed subsection 12., Miscellaneous:

Delete comma after "systemic". [...for systemic dermatomyositis..]

d. GENERAL

Seventh paragraph, first sentence:

...infections; diverticulitis..[delete semi-colon and add a colon]

e. ADVERSE REACTION

Center section title "ADVERSE REACTIONS"

f. DOSAGE and ADMINISTRATION

Seventh paragraph, second sentence:

Add a comma after the word "suffice".
[...generally suffice, while...]

g. HOW SUPPLIED

i. Refer to comment (iii.) under DESCRIPTION.

ii. First sentence:

...each 5mL.[add (teaspoonful)]as does the reference listed drug.

iii. Revise the first sentence to read as follows:

...each 5mL(teaspoonful) and is supplied in 8oz.(236mL) and 16oz.(473mL) bottles.

iv. See statement under GENERAL COMMENTS.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Telecon

Date: 121297

Time: 1500

ANDA #: 40-287

Firm: Halsey Drug Company

Drug: Prednisolone Syrup USP, 15 mg/mL

Participants: Gregg Davis, FDA and George Scholes, Halsey

Agenda:

I called George with concerns about his submission. Flavor Cherry WL-1093 is present in the formulation at a concentration of mL. Upon searching the IIG and COMIS, the highest concentration approved in a previous drug product was mL. With a specific gravity of mcL equates to mg per 5 mL. mg/5mL of Flavor Cherry WL-1093 represents a % increase in what has been previously accepted in an approved drug product. Therefore, the appl. cannot be accepted for filing without data to show that the concentration of the flavor does not affect the safety of the proposed drug product as per 21 CFR 314.94 (a)(9)(ii). This issue is not ordinarily an issue handled on the telephone but because of the next issue, the units may have been suspect so a formulation error may not have been real.

The next issue was a revision of the qualitative and quantitative composition statement. The heading of pg. 95 is "per unit" with units of kg/L. However, the concentrations listed are per 5 mL. The units of "per unit" should be mg/5 mL. Next, the comparative composition statement has some errors that need revising. First, the same issue applies in that the units for "per unit" should be mg/5 mL. Also, the columns marked "per unit" do not list the inactive ingredients in the same concentrations. In the first column, propylene glycol is listed as mg but in the second column, it is listed as mg. Further down the first column, it states that benzoic acid is present at mg but in the second, it lists benzoic acid at a concentration of mg. Lastly, the cherry flavor per ANDA batch is listed as **kg** when it is actually present at **g**.

The last issue is the application has failed to provide the address of the active drug substance manufacturer. It merely states that it is produced by Pharmacia and Upjohn. Also, the

cation has failed to provide the addresses of the inactive redient manufacturers.

George stated that he will confer with the reg. affairs people at Halsey and with the product chemists. He will get back to me after they've talked.

APPEARS THIS WAY
ON ORIGINAL

Telecon

Date: 12/16/97

Time: 1315

ANDA #: 40-287

Firm: Halsey Drug Company

Drug: Prednisolone Syrup USP, 15 mg/mL

Participants: Gregg Davis, FDA and George Scholes, Halsey
Joe Mastranady, Halsey

Agenda:

I called George and told him that the info was not sufficient to justify a technical review of the application. I told him his alternatives were to:

a) re-formulate with an inactive ingredient in a concentration that has been previously approved in a drug product before.

b) provide information justifying the concentration of the inactive by providing other drug products that use that inactive ingredient at that concentration or higher.

c) provide toxicology data justifying the high concentration of that ingredient

Telecon

Date: 041098

Time: 1000 H

ANDA #: 40-287

Firm: Halsey Drug Company

Drug: Prednisolone Syrup USP, 15 mg/mL

Participants: Gregg Davis, and George Scholes, Halsey

Phone #: 718-467-7500

Agenda:

I called George and asked for some revisions. In his response to my RTF letter, there were some errors in their tables. I asked George to revise the quantities of propylene glycol and cherry flavor in exhibits 3 and 4. He said he will fax the info and follow with a hard copy.